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The role of IL-13 and its receptor in allergy and inflammatory responses

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IL-13 is a cytokine that is produced by different T-cell subsets and dendritic cells. IL-13 shares many biologic activities with IL-4. This is due to the fact that IL-13– and IL-4–receptor complexes share the IL-4–receptor α-chain, which is important for signal transduction. T cells do not express functional IL-13 receptors. This is the reason why IL-13, in contrast to IL-4, fails to induce T_{H2}-cell differentiation, one of the hallmarks of the allergic response. However, IL-13 is required for optimal induction of IgE synthesis, particularly in situations in which IL-4 production is low or absent. On the other hand, IL-13 inhibits proinflammatory cytokine and chemokine production in vitro and has potent antiinflammatory activities in vivo. From these observations, it can be concluded that IL-13 is an antiinflammatory cytokine that plays a unique role in the induction and maintenance of IgE production and IgE-mediated allergic responses. (J Allergy Clin Immunol 1998;102:165-9.)

The interaction between cytokines and their receptors on hematopoietic and other cell types plays an important regulatory role in the complicated network of cellular interactions that result in immune and inflammatory responses. Herein, the role of the cytokine IL-13 and its receptor in processes relevant for allergy and inflammation is summarized.

IL-13 was first cloned in the mouse in 1989 by differential hybridization of cDNA libraries of activated T_{H1} and T_{H2} cells, whereas its human homologue was cloned by 2 different groups in 1993. IL-13 consists of 132 amino acids and has a molecular mass of 12 kd. The human IL-13 gene is located on chromosome 5 q 31, in the same 3000 kb cluster of genes encoding IL-3, IL-4, IL-5, IL-9, and GM-CSF. The IL-13 gene is only 12 kb upstream of the IL-4 gene and is positioned in the same orientation, indicating that a gene duplication event took place during evolution. Although the IL-13 protein has approximately only 25% homology with IL-4, it shares many structural characteristics with IL-4. In addition, it shares many, but not all, functional properties with IL-4 that are determined by common IL-4 and IL-13 receptor components expressed on various cell types.[1]

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Abbreviations used
DC: Dendritic cell
VCAM-1: Vascular cell adhesion molecule

IL-13 RECEPTOR COMPLEXES

IL-13R is expressed on B cells, monocytes, macrophages, basophils, eosinophils, mast cells, endothelial cells, keratinocytes, and certain tumor cells, such as renal cell carcinomas and glioblastomas, but thus far no functional receptors have been detected on human T cells or mouse B cells. IL-13R is usually present at 200 to 3000 sites per cell and binds IL-13 with high affinity (Kd 30 pmol/L). The high-affinity IL-13R complex consists of the 140-kd IL-4Rα chain, which binds IL-4 but not IL-13, and an IL-13 binding protein. Two different cDNAs encoding IL-13–binding proteins have been cloned recently and designated IL-13Rα1 and IL-13Rα2.[2, 3] The genes encoding these receptors are both mapped on the X chromosome. IL-13Rα1 consists of 427 amino acids and binds IL-13 with low affinity (Kd ~4 nmol/L). IL-13Rα2 is a 380 amino acid protein, which binds IL-13 with high affinity (Kd ~50 pmol/L) in the absence of the IL-4Rα chain. The human IL-13Rα1 and IL-13Rα2 chains are 27% homologous and are expressed as 65 to 70 kd glycosylated molecules.

The classical IL-4R complex, consisting of the IL-4Rα chain and the common γ-chain (γc), a shared component of the receptors for IL-2, IL-4, IL-7, IL-9, and IL-15, is specific for IL-4. On the other hand, the IL-4 Rα chain is also part of the IL-13R complex because mAbs directed against the IL-4Rα chain inhibit the binding and the biologic activities of both IL-4 and IL-13, suggesting that the IL-4Rα chain is important for signal transduction. This notion was confirmed by the observation that an IL-4 mutant protein, which binds with high affinity to the IL-4R without receptor activation, blocks IL-4– and IL-13–induced IgE synthesis in vitro and in vivo.[5]

Studies with T and B cells from patients with X-linked severe combined immunodeficiency, who have mutations in their γc gene, showed that the IL-13R also functions as a second receptor for IL-4. In addition, these studies suggested that γc are not part of IL-13R complexes. T cells of X-linked patients with severe combined immunodeficiency cannot respond to IL-2, IL-4, IL-7, IL-9, and IL-15, which

accounts for the severe immunologic abnormalities observed in these patients. In contrast, B cells of these patients proliferated and produced IgE in response to CD40 stimulation in the presence of IL-4 or IL-13, indicating that both IL-4 and IL-13 can mediate their biologic effects through the IL-13R complex in the absence of a functional γc-chain. IL-4 and IL-13 signaling in the absence of γc has also been observed in renal cell carcinoma and glioblastoma cell lines, which seem to express high levels of IL-13Rα1 and/or IL-13Rα2, but no IL-4Rα chains.[6]

IL-13 SIGNAL TRANSDUCTION

IL-13R and IL-4R complexes share the signal transducing IL-4Rα chain. Therefore binding of IL-13 or IL-4 to IL-4R and IL-13R results in comparable signaling pathways. Both cytokines activate the JAK-1 and Tyk 2 kinases and induce tyrosine phosphorylation of the IL-4Rα chain and the 170-kd insulin receptor substrate-2, which is the docking site for the Scr homology (SH2) domain containing the 85-kd subunit of PI-kinase in lymphoid cells. In contrast to IL-4, IL-13 does not induce the activation of JAK-3 kinase, which associates with the γc of the IL-4R complex after IL-4 binding. Phosphorylation of the IL-4Rα chain after binding of IL-13 to the IL-13R complex and IL-4 to the IL-4 and IL-13R complexes results in the recruitment, phosphorylation, and nuclear translocation of signal transducer and activator of transcription-6 and the activation of IL-13– and IL-4–responsive genes in various cell types expressing IL-13R and IL-4R complexes.[7]

IL-13 PRODUCTION

Relatively high levels of IL-13 are produced by CD4+ T_{H2} cells after activation. In addition, T_{H0} and CD8+ T cells produce considerable levels of IL-13.[8] In contrast to IL-4, IL-13 is also produced by naive CD45RA+ T cells and T_{H1} cells, albeit at lower levels.[8-10] However, addition of IL-4 further enhanced the percentages of IL-13–producing cells. These observations indicate that IL-13 is not typically a T_{H2} cytokine and that IL-13 production does not require IL-4. The latter notion was confirmed by the observation that IL-13 production is also observed in IL-4–deficient mice after challenge with *Onchocerca volvulus* antigen.[11]

IL-13 is produced early after T-cell activation, and steady state levels of IL-13 mRNA reflecting ongoing IL-13 production can still be observed 72 hours after activation. In contrast, IL-4 production is transient, and generally no detectable levels of IL-4 mRNA can be observed 12 hours after activation of human T-cell clones in vitro.[8] Thus it appears that IL-13 is an abundant cytokine that is produced early and for prolonged time periods by various human T-cell subsets after activation.

IL-13 is also produced in low quantities by EBV-transformed B-cell lines, B-cell lymphomas, keratinocytes, mast cells, and basophils. Interestingly, IL-13 is, in contrast to IL-4, also produced by dendritic cells (DCs) isolated from tonsillar germinal centers.[12] Although the role of IL-13 in DC functions and DC differentiation remains to be investigated, it may contribute to the regulatory function of DCs on B-cell proliferation and differentiation.

BIOLOGIC ACTIVITIES OF IL-13

IL-13 shares many, but not all, of its biologic activities with IL-4, which is not surprising taking into account that IL-4R and IL-13R complexes share the IL-4Rα chain required for signal transduction.

IL-13, in contrast to IL-4, does not support the proliferation of activated human and mouse T cells. More importantly, IL-13 was unable to drive the differentiation of naive CD4+ cord blood T cells into a T_{H2} phenotype.[13] These results indicate that T cells do not express functional IL-13R, which is consistent with the notion that activated human T cells and T-cell clones failed to bind detectable levels of radiolabeled IL-13. However, recent data have indicated that T cells do express IL-13Rα1–chain transcripts intracellularly, but whether this results in the secretion of soluble IL-13Rα chains remains to be determined. Although IL-13 failed to have direct effects on T cells, it may affect T-cell functions and T_{H1}-cell differentiation indirectly through its downregulatory effects on the production of proinflammatory cytokines, particularly of IL-12 by monocytes (see below), which direct T_{H1} development.

REGULATION OF B-CELL FUNCTIONS AND IgE SYNTHESIS

IL-13 has largely similar effects on human B cells as IL-4, but its effects are generally less potent. No additive or synergistic effects are observed when both cytokines are added at optimal concentrations.

IL-13 upregulates the expression of CD23, CD71, CD72, sIgM, and class II MHC antigens. In addition, it has growth-promoting effects on normal B cells activated by anti-IgM or anti-CD40 mAbs and prevents apoptosis of these cells. IL-13 also enhances the production of IgM, IgG, and IgA.[1] The importance of IL-13 as an inducer of allergic responses is reflected in its capacity to induce IgE synthesis by human B cells cultured in the presence of activated CD4+ T cells or anti-CD40 mAbs (Fig. 1).[14]

IL-13–induced IgE synthesis is preceded by induction of germline ε transcription, which is a prerequisite for subsequent IgE switching and IgE production. IL-13 also induces IgM, total IgG, IgG4, and IgE synthesis by highly purified fetal B cells or pre-B cells in the presence of anti-CD40 mAbs or activated CD4+ T cells or activated CD4+ T-cell clones and IL-7, respectively, although IL-13, in contrast to IL-4, did not enhance CD23, CD40, and HLA-DR expression or induce germline ε expression by pre-B cells in the absence of other stimuli.[15] These results suggest that IL-13R is expressed later during B-cell ontogeny than IL-4R. Although IgE is not spontaneously produced by B cells in early fetal tissues, IgE can be detected in cord blood, and increased cord blood IgE levels are associated with a family history of atopy and increased risk of allergies early in life. Elevated IgE levels in cord blood are associated with maternal atopic disease, suggesting that IL-4 and IL-13 produced by the mother may cross the placenta. However, the observation that IL-4, in contrast to IL-13, directly acts on pre-B cells suggests that IL-4, rather than IL-13, may induce commitment to enhanced IgE synthesis during

intrauterine life and may explain the increased IgE production in neonates of atopic mothers.

Although IL-4 and IL-13 both induce IgE synthesis in vitro, the relative contribution of the 2 cytokines to IgE production in vivo remains to be determined. Such studies are hampered by the lack of suitable animal models because IL-13, in contrast to IL-4, does not act on murine B cells. Initially, it was reported that IL-4–deficient mice are unable to produce IgE in vivo. However, more recent studies indicated that these mice can produce low levels of IgE after infection with *Plasmodium chabaudi* or *Leishmania major*, indicating that IL-4–independent mechanisms of IgE induction are operational.[16] Whether IL-13 accounts for these effects is currently not known because thus far it has not been shown that IL-13 induces IgE switching in murine B cells. These data are in line with the observation that mouse B cells do not express detectable levels of IL-13R and imply that no conclusions on the relative roles of IL-4 and IL-13 in inducing IgE synthesis can be drawn on the basis of the results obtained in this mouse model.

Early studies indicated that IgE synthesis induced by T cells from atopic patients was only partially dependent on IL-4. More recently, it has been shown that neutralization of both IL-4 and IL-13 activities in supernatants of activated allergen-specific T_{H2} cells with anti-IL-4 or anti-IL-13 antibodies is required for complete inhibition of IgE synthesis, but that IL-4 is the dominant cytokine in this process. Interestingly, IL-13 particularly contributed to IgE synthesis induced by supernatants of allergen-specific T_{H2} cell lines obtained from skin biopsy specimens from patients with atopic dermatitis, which, in addition to IL-4, produced relatively high levels of IL-13. IgE production induced by supernatants of T_{H1} or $CD8^+$ T-cell clones was completely blocked by anti-IL-13 mAbs, indicating that IL-13 is the dominant IgE-inducing cytokine in situations where IL-4 is absent or present at low levels (eg, during the initiation of allergic responses).[17] This notion is consistent with the observation that IL-13, but not IL-4, is produced by naive T cells. On the basis of these results, it is tempting to speculate that IL-13 produced by virus-specific $CD8^+$ T cells induces IgE synthesis and contributes to the exacerbation of asthma caused by viral infections. These data, and the observations that IL-13 expression is upregulated in atopic skin, in the lungs of patients with asthma, and in patients with chronic sinusitis and is downregulated in response to corticosteroid therapy, underscore the unique and important role of IL-13 in the regulation of atopic and allergic responses.

THE ROLE OF IL-13 IN INFLAMMATORY PROCESSES

IL-13 has dual effects on monocyte/macrophage functions. It enhances the expression of various adhesion molecules on human monocytes, such as CD11b, CD11c, CD18, CD29, and CD49ε (very late antigen-4), which probably contributes to enhanced extravasation, mobility, and trafficking of these cells. Therefore it is not unexpected that IL-13 also acts as a chemoattractant for monocytes. IL-13 furthermore enhances the expression of class II MHC antigens and of CD80 and CD86, the ligands for CD28 on T cells, which results in an enhanced capacity to stimulate alloantigen-specific T cells in vitro.[1] IL-13 also induces the low-affinity receptor for IgE (CD23), which, through its capacity to focus allergen/IgE complexes to allergen-specific T cells, is thought to enhance allergic responses in vivo. Long-term culture of monocytes and macrophage precursors in the presence of IL-13 and GM-CSF results in the differentiation of DCs and therefore may contribute to the generation and maintenance of the DC compartment.

In addition to these immunostimulatory properties, IL-13 has important antiinflammatory properties. IL-13 enhances the production of IL-1Rα and induces the release of the "decoy" IL-1RII. These molecules effectively bind IL-1 and therefore have antiinflammatory activity.[16] IL-13 also effectively downregulates the production of proinflammatory cytokines (eg, IL-1α, IL-1β, IL-6, and TNF-α) and chemokines (eg, IL-8, macrophage inflammatory protein-1α and 1β, and monocyte chemotactic protein-3) by activated monocytes and alveolar and synovial macrophages from patients with rheumatoid arthritis (Fig. 1). The antiinflammatory activities of IL-13 are further exemplified by its capacity to modulate, directly or indirectly, various mediators of inflammation. For example, IL-13 induces the expression of 15-lipoxygenase, which catalyzes the formation of 15-S-HETE and lipoxin A4, mediators that antagonize proinflammatory leukotrienes. IL-13 also inhibits the formation of PGE-2 from arachidonic acid through the inhibition of Cox-2 induction in activated monocytes. Furthermore, the production of NO by LPS-activated mouse macrophages and mesangial cells and superoxide anion production by human monocytes is inhibited by IL-13.[1,16]

Furthermore, IL-13 has potent antiinflammatory activities in vivo. It could rescue mice from LPS-induced lethal endotoxemia, which correlated with downregulation of TNF-α, IFN-γ, and IL-12 production. However, it remains to be determined whether endogenously produced IL-13 has a protective role in sepsis because no detectable levels of IL-13 could be observed in sera from septic patients. In addition, a single injection of CHO cells transfected with IL-13 reduced both the severity and incidence of collagen-induced arthritis in mice, which correlated with reduced TNF-α production by spleen cells. IL-13 was also effective in experimental autoimmune encephalomyelitis (EAE) models as judged by a reduction in duration, severity, and incidence of the disease. Although EAE is primarily a T-cell mediated disease, this is not a surprising observation and can be explained by the downregulatory activity of IL-13 on the production of IL-1 and TNF-α, which have been shown to be associated with the neurologic sequelae of the disease. Similarly, intratracheally administered IL-13 suppressed IgG-immune complex–induced acute lung injury in rats. This was associated with a strong downregulation of TNF-α production and an inhibition of neutrophil accumulation in the lungs.[16]

Collectively, these data indicate that IL-13 has potent antiinflammatory activities both in vitro and in vivo.

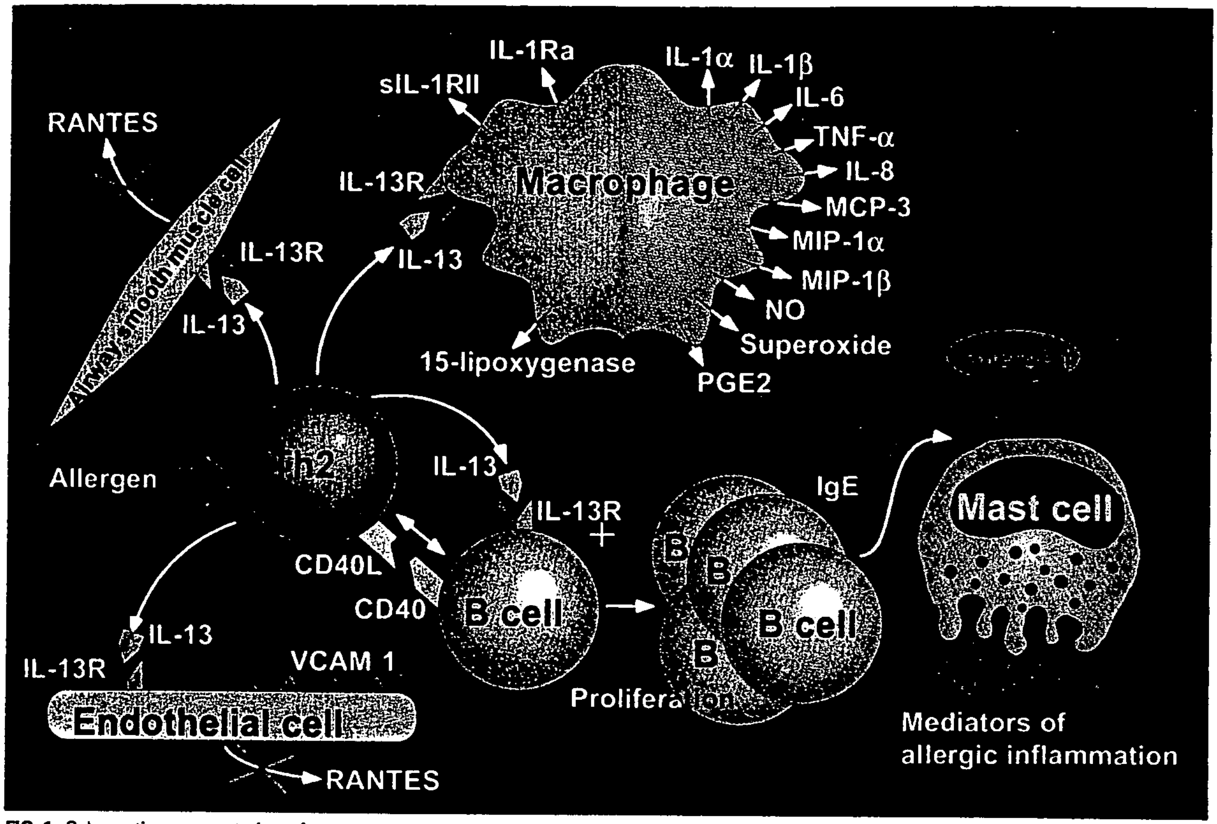

FIG. 1. Schematic representation of some major activities of IL-13 on allergic and inflammatory processes. Stimulation of allergen-specific T_{H2} cells by allergen-derived peptides presented by antigen-presenting cells in the context of class II MHC molecules results in production of IL-13, which binds to IL-13R. IL-13R signaling, together with CD40L-CD40 contact-mediated signals, induced B cells to proliferate and to switch IgE-producing cells. Allergen-specific IgE binds to high-affinity IgE receptors on mast cells and basophils (not shown), which, after cross-linking of IgE/FcεRI complex, results in activation of these cells and release of mediators of allergic inflammation. Binding of IL-13 to IL-13R on activated macrophages induces an antiinflammatory state of these cells. It results in downregulation of proinflammatory cytokines, chemokines, NO superoxide, and PGE-2 production, whereas at the same time it leads to production of IL1-Rα, soluble IL1RII, and 15 lipoxygenase, which have antiinflammatory activities. In addition, IL-13 inhibits production of RANTES, which is a potent eosinophil attractant, by airway smooth muscle cells, endothelial cells, and lung epithelial cells (not shown). On the other hand, IL-13 induces VCAM-1 expression on endothelial cells, which promotes adhesion and extravasation of eosinophils, monocytes, and T cells to sites of allergic inflammation.

EFFECTS OF IL-13 ON ENDOTHELIAL CELLS AND EOSINOPHILS

In addition to its capacity to induce IgE synthesis, IL-13 also contributes to allergic-inflammatory processes through its capacity to induce vascular cell adhesion molecule (VCAM)-1 expression on human umbilical vein endothelial cells.[18] If this results in the adhesion and subsequent extravasation of α4β1 integrin–positive T cells, monocytes, and eosinophil (Fig. 1). IL-13 has no effect on E-selectin or intercellular adhesion molecule-1 expression on endothelial cells and fails to induce neutrophil adhesions and extravasation. Eosinophils accumulate at sites of allergic inflammation under the influence of the chemokine RANTES, which acts as a powerful eosinophil attractant. Recently, it has been shown that RANTES is not only produced by lung endothelial and epithelial cells but also by airway smooth muscle cells after activation with TNF-α.[19] Local RANTES production probably contributes to the accumulation of eosinophils in the lungs of asthmatic patients, where they are thought to contribute to the pathogenesis of the lung inflammation and to cause lung epithelial cell destruction through mediator release. In addition, these data suggest that airway smooth muscle cells participate in chronic airway inflammation by secreting RANTES. IL-13 also acts directly on eosinophils, as judged by induction of CD69 expression on these cells.[16] In addition, IL-13, like IL-5, prolongs eosinophil survival and thereby probably enhances the pathologic effects of these cells at sites of inflammation. Thus the ability of IL-13 to induce VCAM-1 expression on endothelial cells and subsequent interactions of VCAM-1 on endothelial cells and α4β1 integrins on T cells, monocytes, and eosinophils, which leads to the recruitment of these cells and eosinophil survival at sites of allergic inflammation, further emphasizes the importance of this cytokine in the pathogenesis and maintenance of allergic and asthmatic responses.

On the other hand, IL-13 downregulates RANTES expression by airway smooth muscle cells and endothelial cells, indicating that IL-13, in addition to its immunostimulatory activities, has antiinflammatory activities by downregulating the capacity of RANTES to attract T cells and inflammatory cells. How these immunostimulatory and

antiinflammatory processes are spaced in time and locally in the microenvironment in vivo is presently unclear.

CONCLUDING REMARKS

IL-13 has important immunomodulatory activities on many cell types. However, its activities seem to be more restricted than those of IL-4, which is related to the distribution of IL-13R. Most notably, IL-13 does not act on T cells, and therefore in contrast to IL-4, is ineffective in directing T_{H2}-cell differentiation. Induction of allergen-specific T_{H2}-cell differentiation represents the hallmark of allergic diseases because cytokines produced by these cells induce and maintain allergic inflammatory processes. IL-4 and IL-13 produced by allergen-specific T_{H2} cells induce IgE synthesis, whereas IL-5 mediates the growth and survival of eosinophils, which have been implicated in the pathology of asthma. In addition, T_{H2} cytokines synergize with c-kit ligand in promoting the growth and differentiation of mast cells, which, through the release of inflammatory mediators, play an important role as effector cells in allergic inflammation. On the basis of these criteria, it seems that IL-4 is the more dominant cytokine in the induction and maintenance of allergic responses. However, it still needs to be confirmed that IL-13 indeed fails to induce T_{H2}-cell development in models in vivo in which IL-4 is effective.

IL-13 induces IgE synthesis independently of IL-4, and it seems to be required for optimal IgE production, particularly when IL-4 production is absent or low. In this aspect, it is of interest to note that IL-13, in contrast to IL-4, is produced by naive $CD45RA^+$ T cells, which implies that it may play an important role in the initiation of IgE production. IL-13 is also produced by $CD8^+$ T cells. Therefore it seems not unlikely that IL-13 produced by $CD8^+$ T cells expanding in response to viral infections is associated with the well-documented exacerbation of asthma. These observations furthermore indicate that optimal inhibition of IgE synthesis and IgE-mediated allergic responses requires inhibition of both IL-4 and IL-13. The importance of IL-13 as an inducer of allergic inflammatory responses is also supported by its capacity to induce VCAM-1 expression on endothelial cells, which results in the adhesion and subsequent extravasation of T cells, monocytes, and eosinophils to sites of allergic inflammation. In addition, its effects on eosinophil survival probably enhances the pathologic activities of these cells.

Collectively, these observations clearly indicate that IL-13 plays an important role in the induction of allergic responses and contributes to the process of allergic inflammation. However, this function is difficult to reconcile with the antiinflammatory activities of IL-13, particularly on monocytes and macrophages, and its capacity to downregulate RANTES production by airway smooth muscle cells and endothelial cells. The antiinflammatory effects of IL-13 were also observed in vivo. IL-13 inhibits LPS-induced lethal shock, collagen-induced arthritis, EAE, and immunocomplex-induced acute lung injury, diseases in which TNF-α produced by macrophages plays a major role. Balancing these observations, it can be concluded that IL-13 is predominantly an antiinflammatory cytokine, which specifically induces IgE production by B cells and therefore contributes to the initiation and maintenance of IgE-mediated allergic processes.

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